M1438

Effect of Omeprazole on Symptoms and Ultrastructural Esophageal Damage in Duodenogastroesophageal Reflux (DGER)

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Background: The effect of PPI on DGER, even if is a field of interest, it is reported in few studies which are not focalized on the clinical outcome but on pharmacological effects induced by PPI. Recently, it has been demonstrated that dilation of intercellular spaces (DIS) is a very sensitive and early marker of damage in gastroesophageal reflux disease and we have verified his reversibility after PPIs' treatment.
Aim: to valuate whether omeprazole can induce the healing of DIS and regression of symptoms in patients with DGER.
Material and methods: we enrolled 12 patients (4 male; mean age 42.5 ± 9.1yrs, range 26-59) with typical symptoms of esophageal reflux disease and with a pathological 24h pH-metry and bile-monitoring. Patients underwent endoscopy and biopsies were taken from the distal esophagus. Specimens were analyzed at histology and transmission electron microscopy (TEM). Patients were treated with omeprazole 40 mg once daily for 3 months. After this period endoscopy with biopsies was repeated. Subjects with persistent heartburn and/or with an incomplete recovery of DIS, were treated for 3 more months and a new endoscopy was performed.
Results: Eight patients had a normal esophageal mucosa at endoscopy (2 men; mean age 41.1 ± 9.3 yrs) while 4 had erosive esophagitis (2 men; mean age 45.2 ± 9.1 yrs). At histology, among 4 patients affected by erosive esophagitis, 3 had mild esophagitis and 1 moderate esophagitis. No patients with NERD showed histological signs of esophagitis. After 3 months of therapy 11 patients (91.67 %) showed a complete ultrastructural recovery of the mucosa and resolution of heartburn. One patient with erosive esophagitis required 3 more months of therapy because of an incomplete recovery of the epithelium at TEM correlated with sporadic heartburn. The healing of the mucosa was achieved with complete resolution of symptoms.
Conclusions: 3 or 6 months of omeprazole therapy led to a complete regression of the ultrastructural esophageal damage in all patients with DGER. The ultrastructural recovery of the epithelium was accompanied by regression of heartburn in all cases.

M1439

Co-administration of Oral Pentagastrin Enhances the Efficacy of Proton Pump Inhibitors

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Background: Proton pump inhibitors are effective drugs for inhibition of acid secretion. A major limitation in their use is the necessity for proton pump prestimulation and activation to achieve optimal efficacy. Pentagastrin (PG) is known to be such stimulant. However, it is considered inactive following oral administration. Aims: To test whether preactivation of proton pumps by oral PG enhances the anti- secretory effect of omeprazole. Methods: Rats were challenged orally with PG and acid secretion was assessed by measuring pH and acid output. A similar study was repeated in pylorus ligated animals, a model where only a local effect of PG on gastric mucosa is recorded. In further experiments, rats were treated with omeprazole and PG at different sequences. Results: Oral administration of PG significantly increased acid secretion in both non-ligated and in pylorus-ligated rats (ligated rats: control 83 ± 18, post PG 330 ± 11 meq/L $p<0.05$), indicating that PG exerted a direct effect on the gastric mucosa. Co-administration of PG and omeprazole significantly increased gastric pH level compared to omeprazole only (control 2 ± 0.3, omprazole only, 4.4 ± 0.6 omeprazole + PG 5.9 ± 0.2 $p<0.05$). Profound acid inhibition was achieved with either concomitant, or pre-administration of PG, but less so when PG was administered after omeprazole. Conclusion: These data indicate that prestimulation of gastric proton pumps with oral PG enhances the inhibitory effect of omeprazole on acid secretion. This effect is mediated by a local effect of PG. Co-administration of PG and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole.

M1440

Pharmacokinetic and Pharmacodynamic Profiles of AZD0865, a Novel, Potassium-Competitive Acid Blocker

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Purpose: AZD0865 is a substituted imidazopyridine, a novel chemical entity distinct from the substituted benzimidazole proton pump inhibitors that is in development for the treatment of acid-related diseases. We characterized the gastric antisecretory effect of AZD0865 in rat and dog studies, and its pharmacokinetics in dog studies. *Methods:* Stimulated gastric juice was collected in 30-min fractions, and acid output was calculated from titrated acidity and sample weight. AZD0865 was given 2 h or 6.5 h before starting the 2.5 h stimulation (pentagastrin + carbachol) period in chronic fistula rats (n = 8/dose group), and 1.5 h after starting the 6.5 h stimulation (histamine) period in Heidenhain pouch (HP) dogs (n = 4). Plasma samples for analysis of AZD0865 (reversed-phase liquid chromatography and fluorescence detection) were obtained in all dog experiments. *Results:* In the rat, oral administration of AZD0865 caused dose-dependent inhibition of acid output. The oral ED_{50} in the interval 2.5-4.5 h post-dose was estimated at 0.3 μmol/kg. Full antisecretory effect of AZD0865 was established within 2 h post-dose (1 μmol/kg). Almost complete inhibition (≥97%) was maintained for 4.5 and 9 h after 1 and 2 μmol/kg, respectively. In the HP dog, acid output gradually decreased during the first 3 h post-dose and maximum inhibition was reached about 3 h after dose. Acid blockade in the period 3-5 h post-dose was 81 ± 4% after iv AZD0865 (0.25 μmol/kg), and 81 ± 8% and 96 ± 2% after oral doses of 0.5 and 1 μmol/kg, respectively. The oral ED_{50} (95% CI) in dog was estimated at 0.25 (0.14-0.36) μmol/kg. The highest plasma concentration (C_{max}) was observed at 0.5-1 h after oral dose. Oral bioavailability was approximately 50% and plasma half-life ($t_{1/2}$) (calculated up to 5 h or 8 h) was approximately 2 h. After the iv dose, $t_{1/2}$ was 2.0 ± 0.2 h, clearance (CL): 4.3 ± 0.5 mL/kg/min and volume of distribution (V_{ss}): 0.64 ± 0.0 correlation ($r^2 = 0.95$) between maximum inhibition and the log doses, corresponding to an IC_{50} value of 130 nmol/L. Conclus: blocker of stimulated gastric acid secretion in the rat and dc maximum inhibition. In the dog, AZD0865 has a low clearance a: The oral ED_{50} is approximately 0.3 μmol/kg, and almost compl: for 4-5 h after a single dose of 1 μmol/kg. AZD0865 exhibits lir: a simple and predictable dose-response relationship.

M1441

Response to Proton Pump Inhibitors in Non-Cardiac Ch

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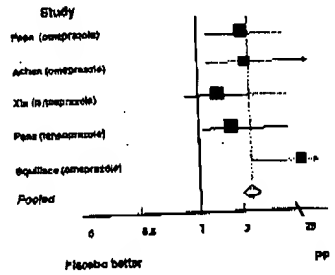
Background and Aims: Non-cardiac chest pain (NCCP) is a con population that negatively impacts on quality of life (Eslı 2003;17:115-24). There are currently no therapeutic approac NCCP. We performed a meta-analysis to test the hypothesis (PPIs) are superior to placebo for inducing symptomatic relief Methods: Search of the electronic databases MedLine and EMBA search from retrieved paper cross-references and from the abstra meetings (1998-2003). The data were extracted independent response was defined as improvement of remission of pain, used to pool the results and the number needed to treat (NN improvement, assessed with symptom diaries or scores.
Results: Five studies using omeprazole (3) or lansoprazole (2) investigated short-term administration of PPIs. The pooled odds to PPIs was 3.51 (95% C.I. 2.11-5.95) and the NNT was 3.7 (was a source of heterogeneity ($p = 0.04$). After removal of the remained significant (3.4, 95% C.I. 1.97-5.96).
Conclusions: Short-term PPIs were superior to placebo in N(



M1442

Early Effects of Tenatoprazole 40 mg And Esomeprаz pH in Caucasian Healthy Volunteers

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Background/aims: Tenatoprazole (TU-199) is a novel proto substantially prolonged plasma half-life, 7-fold longer than the present study was to compare the effects of tenatoprazole 40 mg (E40) on intragastric acidity during the first 48 hours Caucasian volunteers.
Methods: The study had an open label, randomized, crossov negative volunteers received E40 and T40 once daily duri separated by a wash out of at least 14 days. Intragastric pH hours of active treatment using a combined glass electrode logger (Orion, MMS). Meals were standardized for breakfa p.m.) and dinner (at 7.00 p.m.).
Results: During the first 24-hour the median gastric pH T40 than after E40 (3.88 ± 0.78 versus 3.45 ± 0.99 difference reached the statistical level of significance during 2.92 ± 1.26; $p<0.0001$). During the second 24-hour per during the day but there was still a significant difference (4.53 ± 0.95 versus 3.24 ± 1.25; $p<0.0001$). With res spent above the thresholds of pH 3 and pH 4 the same stat in favor of T40 over E 40. For example, the overall tim two consecutive nights was 57 ± 18 % versus 38 ± 14 (($p< 0.0001$).
Conclusion: During the first two days of oral administrati of gastric pH than E40, especially during the night. Whe of nocturnal acidity translates into clinical benefit remai clinical trials.

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